

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

<p>To: Received / Empfangen Ritscher & Partner AG</p> <p>RITSCHER, Dr. Thomas ✓ RITSCHER & PARTNER AG Zollikerstrasse 19 Postfach 372 CH-8029 Zürich SUISSE</p> <p>Dat: <u>19. Jan. 2005</u></p> <p>Ref: _____</p> <p>Frist: <u>1.1.06</u> (F) <i>nat. Phase</i></p>	<p>NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT Rule 71.1)</p> <p>Date of mailing (day/month/year) 17.01.2005</p>	
<p>Applicant's or agent's file reference 7954PCT</p>		
<p>IMPORTANT NOTIFICATION</p>		
<p>International application No. PCT/CH2004/000405</p>	<p>International filing date (day/month/year) 28.06.2004</p>	<p>Priority date (day/month/year) 01.07.2003</p>
<p>Applicant MAX ZELLER SOHNE AG et al.</p>		

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Ladurner, Y

Tel. +49 89 2399-7913



PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT Article 36 and Rule 70)

Applicant's or agent's file reference 7954PCT	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. PCT/CH2004/000405	International filing date (<i>day/month/year</i>) 28.06.2004	Priority date (<i>day/month/year</i>) 01.07.2003
International Patent Classification (IPC) or both national classification and IPC A61K35/78, A61P15/12		
Applicant MAX ZELLER SOHNE AG et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 15 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☒ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 10.12.2004	Date of completion of this report 17.01.2005
Name and mailing address of the international preliminary examining authority: <div style="display: flex; align-items: center;"> <div> European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 </div> </div>	Authorized Officer Pilling, S Telephone No. +49 89 2399-8461



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/CH2004/000405**

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1, 2, 2a, 3, 4, 5, 6, 7, 8, 9, 10, received on 10.12.2004 with letter of 02.12.2004
11, 12

Claims, Numbers

1-9 received on 10.12.2004 with letter of 02.12.2004

Drawings, Sheets

1/1 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/CH2004/000405**

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

see separate sheet

6. Additional observations, if necessary:

II. Priority

1. ☒ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

☒ copy of the earlier application whose priority has been claimed.

☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-5
	No: Claims	6-9
Inventive step (IS)	Yes: Claims	1-5
	No: Claims	6-9
Industrial applicability (IA)	Yes: Claims	1-9
	No: Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/CH2004/000405

Re Item I

Basis of the opinion

1. The amendments filed with the letter dated 02.12.2004 introduce subject matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT. The amendment concerned is the sentence on page 2A stating that *"research leading to the present invention...has shown that... organic acids or gelatine are not very effective in preventing unintended precipitation"*. This sentence appears to extend beyond reporting what is disclosed in the summarised prior art documents and appears to introduce new information about comparative advantages of the invention that was not present in the originally filed application.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability: citations and explanations supporting such statement

2. The documents cited in the International Search Report (ISR) are consecutively numbered D1 to D14 in the order of their listing. If not indicated otherwise, reference is made to the passages cited in said ISR.

Claims 1 to 5

3. None of the presently available prior art documents appears to disclose the subject matter of any of Claims 1 to 5. Thus, the subject matter of Claims 1 to 5 is new (Article 33(2) PCT).
4. The closest prior art appears to be document D1 since this document teaches that the addition of a plant powder such as "*powder of Hydrangeae Dulcis Folium*" to a plant extract prevents deposition of the concentrated extract on the wall of a concentration vessel. Thus, the difference between the disclosure of document D1 and the subject matter of the present invention is the use of polyvinylpyrrolidone (PVP) to prevent deposition. Since there is no data concerning the comparative technical effects of plant powder versus PVP, the objective technical problem to be solved in respect of the present invention appears to be "how to find alternative ways of preventing agglomeration and subsequent precipitation of less soluble components of the primary extract upon concentration" (see present page 4 lines 24 to 28 and the present examples establish the technical effects of PVP). The present solution of using PVP does not appear to be obviously derivable from

document D1. The IPEA does not believe that plant powder and PVP would not normally be recognised as functionally equivalent for the present purpose. There is no teaching in any of the presently available prior art documents toward the use of PVP to prevent agglomeration/precipitation of any plant extracts.

5. Thus, the subject matter of Claims 1 to 5 is inventive (Article 33(3) PCT).

Claims 6 to 9

6. A product is not rendered novel merely by virtue of the fact that it is produced by means of a new process. Hence, Claims 6 to 9 are considered to simply define extracts of *Cimifuga racemosa*, uses thereof and medicaments comprising such extracts. In this regard, the present specification fails to set out any objective criteria or tests by which extracts of *Cimifuga racemosa* obtained by the method of present Claim 1 may be distinguished from extracts of *Cimifuga racemosa* obtained using a prior art method. Thus, since documents D8 to D14 already describe such extracts, uses and medicaments, it is considered that the subject matter of Claims 6 to 9 is not new in view of the disclosures of these documents (Article 33(2) PCT).

10/526972

(7954PCT)

DT01 Rec'd PCT/PTC 07 MAR 2005

PLANT EXTRACTION METHOD AND EXTRACT

The present invention generally concerns the art of producing extracts from medicinal plants and, specifically, production of extracts from medicinal plants which contain a substantial portion, at least, of triterpene glycosides and/or triterpene saponines as active ingredients.

Important examples of this type of medicinal plants are the *Cimicifuga* species, e.g. *Cimicifuga racemosa* (also termed *Actaea racemosa* L.; black cohosh; cohosh bugbane; snakeroot; bugbane) since extracts from various parts of this plant species are known to be effective as analgesics for treatment of pain in muscles and joints, as well as to treat neuralgic diseases rheumatic arthritis, menstrual discomfort, and post-natal pains.

For example, such extracts have been disclosed in WO 99/47149 as an organo-selective estrogen-type medicament for selective treatment and/or prophylaxis of cardiovascular diseases and climacteric discomfort. However, no uterotrophic effects have been observed.

Further, US 6,267,994 discloses use of an extract from *Cimicifuga racemosa*, notably for anti-tumour therapy in compositions that do not exhibit the toxicity of high doses of anti-estrogenic compounds.

Finally, WO 01/05415 discloses a pharmaceutical composition containing components of *Cimicifuga racemosa* extract or derivatives thereof that exhibit an estrogen-type effect.

Conventional methods of producing such extracts are based upon treatment of plant material with an aqueous alcanolic extracting agent so as to obtain a raw or primary extract which after an optional treatment for removal of fines, e.g. by sedimentation or filtration, ~~which~~ contains the extracting agent and the plant constituents that are soluble in the extracting agent.

Typically, the primary extract is then concentrated by partial evaporation of the extracting agent so as to remove its more volatile components, generally the alcanolic constituents plus some water, and to form what is called a concentrated extract, typically containing 5 – 50 % by volume, of residual solvent, i.e. water. Upon further removal of solvent, a solid, pasty, or liquid material is obtained that is substantially free of the solvent used for extraction of the plant material. This product (also termed “ex-

tract") can then be used as such or processed to produce specific application forms^s, e.g. pills, lotions, solutions, powders etc., optionally adding whatever adjuvants, additives, coating components and the like are needed for the final medicinal product.

Research by applicant leading to the present invention has shown that conventional production methods of extracting medicinal plants that contain a substantial portion, at least, of triterpene glycosides and/or triterpene saponines tend to suffer from a loss of active ingredients and/or yield an inhomogeneous product, and that this is due to unintended precipitation upon solvent removal. *Cimicifuga species* are an important example of such medicinal plants but not the only one.

Active ingredients of *Cimicifuga racemosa* include triterpene glycoside of the cycloartan-type of which at least 20 species are known. A main ingredient is acteine, 23-epi-26-deoxyactein, 27-deoxyactin and cimicifugoside A. Actein is a xyloside of acetyl acteol with a 16,23:23,26:24,25-triepoxy side chain. 27-Deoxyactine is used as a standard for quantitative determination of the compounds just mentioned. A further known group of active ingredients are aromatic acids such as ferulic acid, hesperatinic acid and acyl caffeinic acid. Further, the following esters of hydroxy cinnamic acid have been isolated from aqueous ethanolic extracts of *Cimicifuga racemosa*: fucinic acid and the cimicifugic acids A, B, E and F. Flavonoides, biochanine A, formononetin and camphorol have also been reported. Other ingredients are tannins, resins and fatty acids (oleic acid, linolic acid, linolenic acid and palmitinic acid).

With such a large number of constituents it is easily understandable that extraction conditions will have a substantial impact upon the composition of the resulting extracts and that any unintended change of the proportional makeup is undesirable.

Accordingly, it is a first object of the present invention to provide for a new method of extracting such medicinal plants that contain a substantial portion, at least, of triterpene glycosides and/or triterpene saponines, which method is capable of preventing such loss of active ingredients upon solvent removal so as to yield novel extracts of improved composition.

Another object of the invention is an extract of *Cimicifuga species* such as *Cimicifuga racemosa* having a composition that differs from prior art extracts.

A further object of the invention is to provide for medicaments comprising such extracts, as well as for medical treatment of diseases in animal patients including humans using such extracts.

WO 03/000074 and EP 1 407 679 disclose a process for producing a liquid plant extract, e.g. from *Hydrangea dulcis folium* by concentrating a liquid extract in the presence of a plant powder made, for example, from *Hydrangea dulcis folium*.

WO 03/037096 discloses the preparation of extracts from botanic materials wherein at least one acid and an antioxidant, e.g. citric acid and ascorbic acid is added prior to concentration.

According to WO 02/67962 gelatin is added in the preparation and concentration of *Anemone raddeana* extract.

WO 02/30436 discloses extraction of *Phyllanthus* and concentrating the extract after addition of tragacanth gum and maltodextrin.

EP 0 324 197 suggests to use to prepare ginko extract by concentration in the presence of kieselguhr.

Accordingly, the art can be summarized in that various additives, soluble or insoluble in the extraction liquid, have been suggested an used to improve the concentration process when preparing plant extracts. However, research leading to the present invention (cf. example 2) has shown that typical additives, such as organic acids or gelatine, are not very effective in preventing unintended precipitation.

It has been found, according to the invention, that novel extracts including, but not restricted to, those obtainable from various parts of the plant species *Cimicifuga* differing in composition from prior art extracts can be obtained if such unintended precipitation is prevented, and that such prevention can be effected if removal of the extracting solvent is effected in the presence of ^{a polyvinylpyrrolidone (PVP) as} a solution mediator.

Now, according to a first general embodiment the invention provides for a method of producing a vegetal plant extract by the steps of:

- (A) treating a material (e.g. leaves, roots, stems, branches, seeds) of a medical plant, preferably a *Cimicifuga species*, with an extraction agent to obtain a primary extract;
 - (B) separating said primary extract from said solid material; and
 - (C) concentrating said primary extract for removing a portion, at least, of said extraction agent for obtaining an essentially homogeneous concentrate;
- wherein said step (C) of concentrating said primary extract is effected in the presence of an effective amount of ^{PVP as a} pharmacologically acceptable and physiologically inert solution mediator so as to substantially avoid loss of constituents of said primary extract.

According to a preferred embodiment of the inventive method, the product obtained in step (C) is subjected to a further treatment for substantially removing all of the extraction agent, preferably by spray drying, to obtain an essentially dry product.

Medical plants other than *Cimicifuga species* for use in preparing extracts according to the inventive method include *Hedera*, *Liquorice*, *Symphytum*, *Centella asiatica*, *Ginseng* and *Solidago*. Generally, all medical plant extracts can benefit from the inventive teaching of adding a solution mediator prior to concentration provided that the ^{PVP} ~~non-mediator~~ does not form a precipitate with constituents of the extract, e.g. tannic acids, ~~in the case of the preferred solution mediator for *Cimicifuga sp.*~~

Generally, the term "extract" as used herein without further specification is intended to generally refer to any form of the product of extraction minus the extracting agent and regardless of the physical form (i.e. viscous, pasty or solid).

^{AS} ~~PVP~~ suitable solution mediators for use in the invention are macromolecular substances or polymers known to be admissible for use in medicaments and to be physiologically inert as well as soluble in the extraction agent and in water. The term "soluble" as used herein does not necessarily indicate complete solubility but a partial solubility in the extraction agent as well, as is generally apparent from the fact that the ~~solu-~~

~~tion mediator~~ ^{PVP} is capable of being dissolved in the extraction agent at temperatures between 0°C and 100 °C at ambient pressure so as to form a „normal“ (clear) or „colloidal“ (turbid) solution, also termed a colloidal or molecular dispersion. Preferably, the ~~solution mediator~~ ^{PVP} should be capable of forming an aqueous solution which, at room temperature, contains at least about 30% by weight of the ~~solution mediator~~ ^{PVP}.

The molecular mass of such a ~~polymer solution mediator~~ ^{PVP} generally is in the range of from about 1'000 to about 1'300'000 Dalton. A minimum molecular mass of suitable ~~solution mediators~~ ^{PVP} of about 5'000 Dalton is preferred for many purposes of the invention.

10 ~~/According to the invention, a group of preferred solution mediators for alcanolic or alcanol/water as extraction agents is the family of compounds known as poly(vinyl pyrrolidone) also known as povidone or PVP. Such polymers admitted under current food and drug regulations for pharmaceutical or food use are available commercially from various sources.~~ ^{PVPs are and)}

15 As has been shown in many studies, PVP when ingested by humans has no negative effects and is not digested or metabolized. When taken orally, the predominant portion thereof is excreted within 11 hours and no PVP enrichment has been observed.

~~While PVP is preferred for use in polar extraction agents including those containing water, other water soluble polymers of synthetic, semi-synthetic or natural provenience can be used as solution mediators according to the invention, e.g. polyvinyl alcohol as well as cellulose derivatives that are soluble or, at least, capable of swelling in water and the like polymers, as long as they are physiologically inert, i.e. do not significantly affect the human organism when ingested.~~

20 Addition of a ~~solution mediator, such as PVP,~~ not only prevents agglomeration and subsequent precipitation of less soluble components of the primary extract upon concentration in the manner of a protective colloid but additionally ^{is able} to retain the entire content of the plant extract upon complete removal of the extraction agent without loss of extracted plant components.

^{PVP}
30 An effective amount of ~~solution mediator according to the invention~~ generally is in the range of from about 5 % by weight to about 50 % by weight, based upon the weight of the final extract. A range of from about 15 % by weight to about 35 % by weight, is preferred for many purposes.

Preferably, the extraction agent is a polar substance, such as a normally liquid alcohol, e.g. methanol, ethanol, propanol, butanol as well as mixtures of such C₁₋₄ alcohols with each other and/or with water. Mixtures of from about 40 to about 80 %, by weight, of such alcohol, preferably ethanol, with about 60 to about 20 %, by weight, of water are preferred for many purposes. Whenever the qualifier "about" is used herein, it is intended to include a variation of $\pm 30\%$, preferably $\pm 10\%$, from the value associated with this qualifier.

~~Other solution mediators have been found to be effective, however, generally less so in obtaining extracts from *Cimicifuga sp.* Examples of such other solution mediators include: hydroxyethyl cellulose (optionally in mixture with lecithin), maltodextrin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, fructose, tartaric acid (optionally in the form of a salt, e.g. sodium salt).~~

Preferably, the ^{PVP} solution mediator is added to the primary extract rather than to the extraction agent. The extraction procedure may be carried out in conventional apparatus. In any case, the solution mediator is added prior to any significant removal of extraction agent. Such removal or concentration can be effected in a known manner, e.g. by distillation at an elevated temperature and/or reduced pressure taking care to avoid conditions that could affect the components of the extract. Concentration may be effected at constant or varying conditions of temperature and/or pressure.

A preferred embodiment of the inventive process is carried out by extraction of the dry plant material with an ethanol-water mixture containing about 50 - 60 %, by volume, of ethanol and about 50 - 40 %, by volume, of water. Upon concentration, the alcanolic constituents plus any water of an azeotropic mixture is removed until a solids concentration of about 25 - 50 %, by weight, is reached. The concentrated extract obtained may then be processed in any conventional manner, e.g. by spray-drying to form a dry product. During such a final concentration step, e.g. upon spray-drying the solution mediator ^{PVP} ~~such as PVP~~, additionally acts as a spray-drying adjuvant. Generally, the ~~solution mediator~~ has the effect that a homogeneous consistence of the extract is maintained in all stages of the concentration process.

Extracts of *Cimicifuga racemosa* obtained as disclosed herein can be used according to the invention for production of a medicament suitable for treating climacteric and post menopausal distress. Such preparation can be effected in conventional manner

except that the extract used has been obtained in the presence of ^{PVP} ~~the solution mediator~~ according to the invention.

Such a medicament is suitable as a substitute or complement of a hormone replacement therapy, and is capable of alleviating climacteric and menopausal symptoms, therefore it can generally be applied for treating climacteric and post menopausal distress in a female human patient.

A medicament according to the invention normally contains the novel extract as an at least dominant portion in combination with other conventional and well-known components of medicaments which, in turn, may but need not be pharmaceutically active. On the other hand, a medicament according to the invention may substantially consist of the novel extract, e.g. in a liquid or solid diluent.

It has been found according to the invention that the physiological effectiveness of the novel extract can be determined by a relatively simple measuring method, namely by measuring the pulse frequency of an epithelia sample taken from the oviduct as known in the art of determining the effectiveness of hormone treatment (e.g. Mahmood, T. et al. "The effect of ovarian steroids on epithelial ciliary beat frequency in human fallopian tube" (1998), Human Reproduction, 13(11); 2991 – 2994).

The extract according to the invention can be used to prepare medicaments with an effect similar to that of progesterone effective for treatment of climacteric or postmenopausal discomfort in female human patients. To this end, the extract according to the invention can be processed, in a manner known per se from standard pharmacological practice to obtain conventional application forms and applied for medical treatment in the dosages known for use of conventional extracts of *Cimicifuga racemosa*, e.g. in the broad range of from about 0.1 to about 100 mg/kg of body weight. Clinical tests in treating female human patients with menopausal syndrome (cf. example 5 below) gave favorable results when used at a dosage of 6.5 mg and 13 mg/day.

The invention will now be explained in more detail with reference to the enclosed drawing in which:

5 Figure 1 is a diagram of an LC-analysis of a conventionally prepared extract of *Cimicifuga racemosa*;

Figure 2 is a diagram of an LC-analysis obtained under the same general conditions as in Fig. 1, however with an extract of *Cimicifuga racemosa* obtained according to the invention by concentration in the presence of a solution mediator; and

10 Figure 3 is a diagram showing results of clinical testing.

In the following examples given by way of illustration not limitation, indications in percent or parts are based upon the weight unless specifically mentioned otherwise.

15 **Example 1**

Preparation of the extract

Dry root material of *Cimicifuga racemosa* (rhizome) were processed by milling to obtain a powder and charges of material from different harvests were combined for homogeneity.

20 Extraction was performed on the basis of a ratio of 2'500 parts extraction agent per 500 parts of *Cimicifuga racemosa*. The extraction agent, in turn, was prepared by mixing 1'330 parts of ethanol (96%, by volume) and 1' 170 parts of de-ionized water.

Water and ethanol of ambient temperature were mixed in a container provided with a mechanical stirrer and a withdrawal port at the bottom of the container. Then, the
25 *Cimicifuga racemosa* powder was added with continued stirring, and stirring was continued for 300 minutes. Then, the stirrer was stopped and the solids allowed to settle which normally takes about 180 minutes and, in any case, is continued until a clear supernatant has been formed above the sediment.

The clear supernatant is removed by means of a pump and collected in a separate
30 container. The sediment is fed into a filter press to recover additional extraction liquid which is combined with the supernatant and the resulting mixture is fed through a filter into a mixing container provided with a stirrer and a weighing device. After starting of the poly(vinylpyrrolidone) (termed PVP herein, a commercial product sold under the

trade name Plasdone® KW 29-32) is added in an amount of 33 parts per 100 parts of extraction liquid and stirring is continued until the PVP has dissolved and a clear brown liquid is obtained as a first product.

5 This product is fed into a standard-type two-stage concentrator plant type KV 102 EX produced and sold by Unipektin AG, Eschenz, Switzerland, in which the extraction liquid including the PVP is concentrated by evaporation of the extraction agent to yield a dark brown concentrate having a concentration of at least about 9% solids which is then further concentrated to form a spissum extract having a solids content between about 18 and 26 %. Then, the concentrate is fed into a conventional spray-dryer to produce a dry extract in the form of a powder with a humidity content of not more than about 5% by weight.

10 Both the concentrated liquid spissum extract as well as the dry pulverulent extract can be standardized as required and used as or in medicaments according to the invention, for example by producing tablets containing 5 – 50 mg extract and the usual solid diluents, additives, and adjuvants for production of tablets having a final weight of about 100 – 200 mg.

Example 2

~~/Selection of solution mediators/~~

20 Various substances were tested for their effectiveness as solution mediator or protective colloid during concentration. To this end, the criterion of "rimming" was used, i.e. the formation of a distinct "rim" (solidifying deposit at the periphery of the test liquid in a generally round container).

25 Such rimming normally occurs when concentrating a solution that contains an amorphous or resinous solid and indicates commencement of solidification upon concentration by evaporation of the solvent.

30 Research leading to the invention has shown that concentration of a solution of plant extract, notably of *Cimicifuga racemosa*, in the extraction liquid by evaporation leads to formation of a "rim" or "border" upon progressing increase of concentration of the solution, and that such rim tends to contain a substantial portion of the active ingredients of the extract. The result of rimming is that rim solids tend to be discarded because a homogeneous product is to be achieved. As a consequence, final extracts ob-

tained by conventional evaporation do not any longer have the same proportional composition as the primary extracts prior to concentration.

On the other hand, it has been found according to the invention that rimming can be prevented or minimized to insignificance if the solution contains ^{PVP as} what is called a solution mediator herein, and at a concentration which is sufficient to avoid "rimming".

Thus, the effectiveness of a ^{PVP} given substance as a solution mediator for use according to the invention can be determined by a few and simple experiments by observing the amount of rimming and its dependence upon the relative amount of ^{PVP} the substance tested for use as a solution mediator for a given concentration process.

10 In such experiments, ^{PVP} poly(vinylpyrrolidone), also known as ^{PVP or} Povidone, is found to substantially preclude rimming when concentrating extracts of *Cimicifuga racemosa* and, therefore, is the ^{most preferred} solution mediator ^{according to the invention} for processing extracts of *Cimicifuga racemosa* by evaporation of the extraction solvent. A PVP preferred for many purposes of the invention is obtainable commercially under the trademark Plasdone® K-29/32. This PVP has a molecular mass of about 58'000 Dalton units and a typical viscosity 2,5 mPa·s when measured at standard conditions. This type of PVP highly soluble in water as well as in a lower alkanol, methylene chloride, chloroform and other conventional organic solvents.

Another advantage of PVP is that it is an advantageous additive for processing of solid extracts, such as of *Cimicifuga racemosa*, because – since it can be allowed to remain in the final extract products because of its physiological inactivity – it will facilitate shaping methods of the type used in the production of pharmaceutical tablets. Test with PVP indicate that it can be effectively used in an amount of about 5 to about 50 % by weight, based upon the weight of the final extract or product. A range of from about 15 to about 35 % on the same basis has been found to be particularly effective.

Other substances tested but found to be ~~usable but~~ less effective for extracts of *Cimicifuga racemosa* were hydroxyethyl cellulose (optionally in mixture with lecithin), maltodextrin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, fructose, tartaric acid (optionally in the form of a salt, e.g. sodium salt).

Example 3**Analysis of Extract**

The dry extract obtained according to example 1 is a fine lightly brown powder having a characteristic smell. It contains various triterpene glycosides as well as organic acids.

Analytical results of three batches prepared according to example 1 gave the following triterpene glycoside values: 8.34%, 8.84% und 10.04% or an average of 9.07% corresponding to at least 6% if calculated as 27-deoxy acetein, the substance conventionally used for standardization of extracts of *Cimicifuga racemosa*.

These values indicate a most desirable high concentration, notably when considering the fact that the final product contains about 25% of PVP. Conventional extracts of *Cimicifuga racemosa* have a substantially lower content of triterpene glycosides and appear to be less effective at equivalent dosages. The higher and apparently distinctive content of triterpene glycosides in an extract according to the invention is not due to an enrichment procedure but merely upon application of the method according to the invention providing for a recovery of active plant ingredients without loss.

In vitro testing of *Cimicifuga racemosa* extract obtained according to the invention indicates binding to distinguishable somatic receptors as well as to receptors in the central nervous system so as to make such extracts a valuable candidate for alleviating climacteric and menopausal symptoms.

Example 4**Comparative Analyses**

The operation of example 1 was repeated, however once according to prior art, i.e. without use of a solution mediator during concentration (Sample A), and once with addition of PVP as described in example 1 (Sample B).

For analysis, 0.6 g of each sample were extracted with 25 ml during 15 min in an ultrasonic mixer. An aliquot each of test solution A obtained from sample A, and of test solution B obtained from sample B was transferred by means of a syringe filter into a HPLC vial, and 20 µl were injected into the HPLC apparatus. The column used was a reversed phase RP C-18, 3.0 x 120 mm, 3 µm. The mobile phase was a gradient methanol-water with acetonitrile at a flow rate of 1ml/min. Detection was effected by a ELSD device for detection by evaporation light scattering at an evaporation temperature of

50°C and an evaporation pressure of 3.5 bar. The samples were quantified externally against a 27-deoxyactein standard to determine the triterpene glycosides (TTG).

The results are given in Figure 1 for Sample A (prior art extraction method) and in Fig. 2 for sample B (according to the invention; concentration of extract in the presence of solution mediator). As is apparent from a comparison of Fig. 1 and 2, the inventive method provides an extract having a clearly different proportional composition believed to be causal for the advantageous results of clinical testing.

10 Example 5

Clinical Testing

The objective of clinical testing was to evaluate the efficacy and safety of *Cimicifuga racemosa* in the form of tablets prepared from the extract obtained according to example 1 in the treatment of patients with menopausal syndrome.

15 The test was designed as a prospective, randomised, double-blind, placebo-controlled, parallel group comparison.

Test setting was multicentre in four outpatient general medicine clinics.

180 patients as subjects were randomised and evaluated for the intention-to-treat analysis (60 patients in three groups: placebo, *Cimicifuga racemosa* extract 6.5mg, *Cimicifuga racemosa* extract 13mg). Established diagnostic criteria for menopausal syndrome and validated assessment scales were used.

Interventions: *Cimicifuga racemosa* extract tablets, 13mg; OR 6.5mg ; OR matching placebo tablets once-daily for 12 consecutive weeks.

Main outcome measures: All variables were prospectively sought in a Protocol. Statistical analysis was on an intention-to-treat basis. The main efficacy variable was change from baseline to endpoint (end of Week 12) in menopausal symptoms using the Kuppermann Index (K Index) (cf. Kuppermann H.S., "Comparative clinical evaluation of estrogen preparations by the menopausal and amenorrhoeal indices." *J Clin Endocr* 1953; 13: 88). The secondary efficacy variables were: (a) patients' self-assessment of Quality of Life; and (b) Responder Rates. Safety was evaluated by adverse event and clinical laboratory monitoring.

Results: Changes in menopausal symptoms from baseline to end of treatment (main endpoint) were significantly superior for patients receiving *Cimicifuga racemosa* extract

relative to those on placebo ($p < 0.0001$ for 13mg; $p < 0.001$ for 6.5mg). Patients' self-assessment of Quality of Life and responder rates results were similar to those for the main endpoint. Evaluation of menopausal symptoms and Quality of Life showed a high correlation ($r = -0.84$) between the two assessment instruments. The reported adverse events did not raise a safety concern and hormonal levels were not affected by *Cimicifuga racemosa*.

The conclusions from this clinical test can be summarized as follows: As the indication for hormone replacement gradually shifts from prevention of chronic disease to shorter-term symptom relief, *Cimicifuga racemosa* is an effective non-hormonal alternative to hormone treatment in women with menopausal symptoms.

The test results are summarized in Fig. 3 representing the correlation of Quality of Life (on the ordinate in terms of visual analogue scale) versus the Kuppermann-Index (on the abszissa).

While examples were given above, it is to be understood that these examples are for illustration and not limitation, and various changes will be apparent to those experienced in the art of preparing extracts from medical plants.

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CLAIMS

1. A method for producing a vegetal plant extract by the steps of:
- (A) treating a solid plant material with an extraction agent to obtain an extraction liquid containing said extract dissolved in said extraction agent;
- (B) separating said extraction liquid from said solid plant material; and
- (C) concentrating said extraction liquid by at least partially removing said extraction agent to produce a concentrated extract;
- wherein said step (C) of concentrating said extraction liquid is effected in the presence of an effective amount of a pharmacologically acceptable and physiologically inert solution mediator so as to substantially avoid loss of constituents of said extract liquid upon concentration thereof by an at least partial removal of said extraction agent, *said solution mediator being poly(vinylpyrrolidone).*
2. The method of claim 1 wherein said extraction agent is a polar substance and preferably a C₁₋₄ alkanol or a mixture of such alkanol with water.
3. The method of claim 1 or 2 wherein said solution mediator is an organic polymer capable of being colloidally dispersible or soluble in said extraction agent.
4. The method of claim 3 wherein said organic polymer used as said solution mediator has an average molecular mass of at least about 1000 Dalton units.
- ~~5. The method of any of claims 1 - 4 wherein said solution mediator is poly(vinylpyrrolidone).~~
5. The method of any of claims 1 - 4 wherein said vegetal plant is *Cimicifuga racemosa*.

~~6~~
~~7~~ An extract obtained by concentration of an extract fluid obtained by extract-
ing of *Cimicifuga racemosa* with an extraction agent and concentration of said fluid ex-
tract in the presence of an effective amount of a solution mediator as defined in any of
5 claims 1 - ~~5~~.

~~7~~
~~8~~ Use of an extract as defined in claim ~~7~~ ⁶ for production of a medicament ca-
pable of binding somatic as well as central nervous receptors so as to be suitable for
10 treating climacteric and post menopausal distress.

~~8~~
~~9~~ Use of an extract as defined in claim ~~7~~ ⁶ for production of a medicament suit-
able as a substitute or complement of a hormone replacement therapy.

15

~~9~~
~~10~~ A medicament capable of substituting or complementing hormone replace-
ment therapy, said medicament consisting at least in part of an extract obtained by con-
centration of an extract fluid from *Cimicifuga racemosa* in the presence of an effective
20 amount of a ^{PVP as a} solvent mediator.

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